

# Variable Impact on Mortality of AIDS-Defining Events Diagnosed during Combination Antiretroviral Therapy: Not All AIDS-Defining Conditions Are Created Equal

Antiretroviral Therapy Cohort Collaboration (ART-CC)<sup>a</sup>

**Background.** The extent to which mortality differs following individual acquired immunodeficiency syndrome (AIDS)-defining events (ADEs) has not been assessed among patients initiating combination antiretroviral therapy.

**Methods.** We analyzed data from 31,620 patients with no prior ADEs who started combination antiretroviral therapy. Cox proportional hazards models were used to estimate mortality hazard ratios for each ADE that occurred in >50 patients, after stratification by cohort and adjustment for sex, HIV transmission group, number of antiretroviral drugs initiated, regimen, age, date of starting combination antiretroviral therapy, and CD4<sup>+</sup> cell count and HIV RNA load at initiation of combination antiretroviral therapy. ADEs that occurred in <50 patients were grouped together to form a “rare ADEs” category.

**Results.** During a median follow-up period of 43 months (interquartile range, 19–70 months), 2880 ADEs were diagnosed in 2262 patients; 1146 patients died. The most common ADEs were esophageal candidiasis (in 360 patients), *Pneumocystis jiroveci* pneumonia (320 patients), and Kaposi sarcoma (308 patients). The greatest mortality hazard ratio was associated with non-Hodgkin’s lymphoma (hazard ratio, 17.59; 95% confidence interval, 13.84–22.35) and progressive multifocal leukoencephalopathy (hazard ratio, 10.0; 95% confidence interval, 6.70–14.92). Three groups of ADEs were identified on the basis of the ranked hazard ratios with bootstrapped confidence intervals: severe (non-Hodgkin’s lymphoma and progressive multifocal leukoencephalopathy [hazard ratio, 7.26; 95% confidence interval, 5.55–9.48]), moderate (cryptococcosis, cerebral toxoplasmosis, AIDS dementia complex, disseminated *Mycobacterium avium* complex, and rare ADEs [hazard ratio, 2.35; 95% confidence interval, 1.76–3.13]), and mild (all other ADEs [hazard ratio, 1.47; 95% confidence interval, 1.08–2.00]).

**Conclusions.** In the combination antiretroviral therapy era, mortality rates subsequent to an ADE depend on the specific diagnosis. The proposed classification of ADEs may be useful in clinical end point trials, prognostic studies, and patient management.

The reporting of unusual conditions, such as Kaposi sarcoma and *Pneumocystis jiroveci* pneumonia (PCP), among men who have sex with men signalled the arrival of HIV in the early 1980s [1, 2]. A definition for the new syndrome of AIDS was devised in 1985 [3]. The case definition was developed by epidemiologists with the aim of tracking the emerging epidemic. Changes to this surveillance case definition were made in 1987 and 1993, when additional opportunistic infections were

added to the list of AIDS-defining events (ADEs) [4, 5]. Although the case definition of AIDS was never intended for this purpose, researchers adopted AIDS as an end point in clinical research, and clinicians used it as a prognostic marker. Indeed, before the advent of combination antiretroviral therapy (cART), patients who received a diagnosis of AIDS had a poor median survival of 12–18 months [6]. However, there was considerable variation in the duration of survival, depending on the specific diagnosis [7] and the CD4<sup>+</sup> cell count at diagnosis [8].

In the era of cART, clinical trials have continued to use AIDS as a marker of clinical disease progression

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[9–11], although the low incidence of ADEs meant that many studies used changes in HIV load or CD4<sup>+</sup> cell count, rather than the occurrence of AIDS or death, as their main end point. Large cohort studies and collaborations of cohorts used AIDS in prognostic models and risk scores to help clinicians, care providers, and patients to assess short-term and medium-term prognosis after initiating cART [12–14].

Studies that use AIDS as an end point or prognostic factor make an implicit assumption that all ADEs have the same consequence in terms of subsequent morbidity and mortality. To our knowledge, no study to date has had sufficient power to examine the variation in subsequent mortality associated with specific ADEs among patients receiving cART. We analyzed the large database of the Antiretroviral Therapy Cohort Collaboration (ART-CC) to determine the relative importance of different ADEs for subsequent mortality and to rank ADEs in terms of their prognostic importance for patients starting cART.

## METHODS

**ART-CC.** The ART-CC is a collaboration of cohort studies from Europe and North America that was established in 2000 with the aim of describing the prognosis of antiretroviral-naïve patients starting cART. The study design has been described in detail elsewhere [15]. In brief, prospective cohort studies were eligible if they had enrolled at least 100 patients with HIV infection aged  $\geq 16$  years who had not previously received antiretroviral treatment and who had started antiretroviral therapy with a combination of at least 3 drugs, including nucleoside reverse-transcriptase inhibitors, protease inhibitors, or non-nucleoside reverse-transcriptase inhibitors, with a median duration of follow-up of at least 1 year. Cohorts provided anonymized data on a predefined set of demographic, laboratory, and clinical variables, including age, sex, risk group, drugs included in the cART regimen, CD4<sup>+</sup> cell count and viral load at cART initiation and at 6 and 36 months, in addition to the CD4<sup>+</sup> cell count before the diagnosis of an ADE (each CD4<sup>+</sup> cell count was measured within a maximum period of 6 months before the relevant time point).

**Participating cohorts.** Fifteen cohorts contributed data: the AIDS Therapy Evaluation Project Netherlands (3903 patients); the Aquitaine Cohort (831 patients); the British Columbia Centre for Excellence in HIV/AIDS (764 patients); Collaborations in HIV Outcomes Research (924 patients); the EuroSIDA study (92 centres across Europe, Argentina, and Israel; 1315 patients); the Frankfurt HIV Cohort (1436 patients); the French Hospital Database on HIV (13,758 patients); the Italian Cohort of Antiretroviral-Naïve Patients (2428 patients); the Köln/Bonn Cohort (406 patients); the Proyecto para la Informatización del Seguimiento Clínico-Epidemiológico de la Infección por HIV y SIDA (1851 patients); the Royal Free Hospital Cohort (649 patients); the Southern Alberta Clinic (270

patients); the Swiss HIV Cohort Study (2275 patients); the University of Alabama at Birmingham 1917 Clinic Cohort (485 patients); and the University of Washington HIV Cohort (322 patients). All cohorts have been approved by their local ethics committees or institutional review boards, use standardized methods of data collection, and schedule follow-up visits at least once every 6 months.

**Inclusion criteria and definitions.** All antiretroviral-naïve patients with HIV infection who initiated cART before 31 December 2004 but who had not received a prior diagnosis of AIDS were included in analyses. Patient selection and data extraction were performed at the data centers of the participating cohorts. Anonymized data were pooled and analyzed centrally. ADEs were ascertained prospectively by use of the diagnostic criteria outlined in the 1993 AIDS definition [5]. Both definitive and presumptive diagnoses were included in analyses. Type-specific ADEs were combined into a single category; thus, cytomegalovirus retinitis and cytomegalovirus infection of other sites were combined into a single cytomegalovirus infection category. Different types of non-Hodgkin's lymphoma (e.g., Burkitt's lymphoma, primary brain lymphoma, immunoblastic lymphoma, and lymphoma of unknown histology) were also combined into a single category. ADEs that occurred in  $<50$  patients in the combined dataset were grouped together to form a "rare ADEs" category and included coccidioidomycosis (1 diagnosis, 0 deaths), pulmonary candidiasis (15 diagnoses, 6 deaths), histoplasmosis (17 diagnoses, 4 deaths), invasive cervical carcinoma (20 diagnoses, 3 deaths), isosporiasis (7 diagnoses, 0 deaths), salmonella septicemia (7 diagnoses, 2 deaths), unspecified Centers for Disease Control and Prevention type C events (2 diagnoses, 1 death), unspecified tuberculosis (6 diagnoses, 1 death), and bacterial pneumonia (48 diagnoses, 5 deaths).

**Statistical methods.** Cox proportional hazards models, stratified by cohort and adjusted for sex, risk group, age, CD4<sup>+</sup> cell count and viral load at cART initiation, cART regimen, and date of cART initiation were used to estimate the mortality hazard ratio (MHR) after each of the ADEs, compared with the MHR in patients who had not experienced an ADE. Each ADE was treated as a time-dependent covariate, and all ADEs were included in the model simultaneously. The proportional hazards assumption was tested, and there was no evidence of nonproportionality ( $P > .2$ ). Recurrences of the same ADE were not included in analyses. Patients were followed up from the date of cART initiation until death (of any cause). All analyses were intent-to-treat, ignoring treatment interruptions or stopping of antiretroviral therapy. Patients who remained alive were censored at their last visit plus 50% of the median time between visits for each cohort. For example, if a cohort had a median of 6 months between follow-up visits, patients who did not die would be censored at the last visit plus 3 months. The hazard

**Table 1. Demographic and clinical characteristics of 31,620 antiretroviral-naïve patients starting combination antiretroviral therapy.**

Variable	All patients (n = 31,620)	Patients with AIDS (n = 2262)
Percentage of all patients	100	7.2
Age, median years (IQR)	36 (31–43)	37 (32–44)
Sex		
Male	22,730 (71.9)	1729 (76.4)
Female	8890 (28.1)	533 (23.6)
Transmission risk group		
Heterosexual sex	12,545 (39.7)	865 (38.2)
IDU	4786 (15.1)	421 (18.6)
Men who have sex with men	11,361 (35.9)	777 (34.4)
Other	2928 (9.3)	199 (8.8)
Date of starting cART, median date (IQR)	May 2000 (Jun 1998–Mar 2002)	Jun 1999 (Jan 1998–Jun 2001)
Baseline CD4 <sup>+</sup> cell count, median cells/ $\mu$ L (IQR)	256 (145–384)	138 (45–275)
Baseline viral load, median log <sub>10</sub> copies/mL (IQR)	4.84 (4.31–5.30)	5.16 (4.65–5.61)
No. of antiretroviral drugs received		
3	26,163 (82.7)	1807 (79.9)
$\geq 4$	5457 (17.3)	455 (20.1)
Type of cART received		
PI based	18,153 (57.4)	1551 (68.6)
NNRTI based	9765 (30.9)	494 (21.8)
NRTIs only	2937 (9.3)	150 (6.6)
Other	765 (2.4)	67 (3.0)

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. cART, combination antiretroviral therapy; IDU, injection drug use; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

ratios for each ADE were ranked, and bootstrapping was used to derive 95% CIs for these ranks (on the basis of the 2.5th and 97.5th percentiles of ranks in 1000 resampled datasets). ADEs were split into 3 severity groups on the basis of these ranks, and the adjusted MHRs (aMHRs) for mild, moderate, and severe diagnoses were determined after additional adjustment for the number of ADEs diagnosed as a time-dependant covariate.

Patients starting cART may experience a rapid increase in their CD4<sup>+</sup> cell count during the first 6 months of therapy [16], which will affect the subsequent risk of developing an ADE, and ADEs developing within the first 6 months of cART may be caused by immune reconstitution syndrome [17]. Therefore, we performed an additional analysis to estimate the risk of mortality following an ADE diagnosed after this initial period of treatment. Follow-up was censored at 6 months after cART initiation; patients with  $<6$  months of follow-up were excluded, and ADEs that occurred during the initial 6 months after cART initiation were excluded. This analysis was adjusted as described above and was additionally adjusted for the CD4<sup>+</sup> cell count and viral load determined at 6 months after cART initiation.

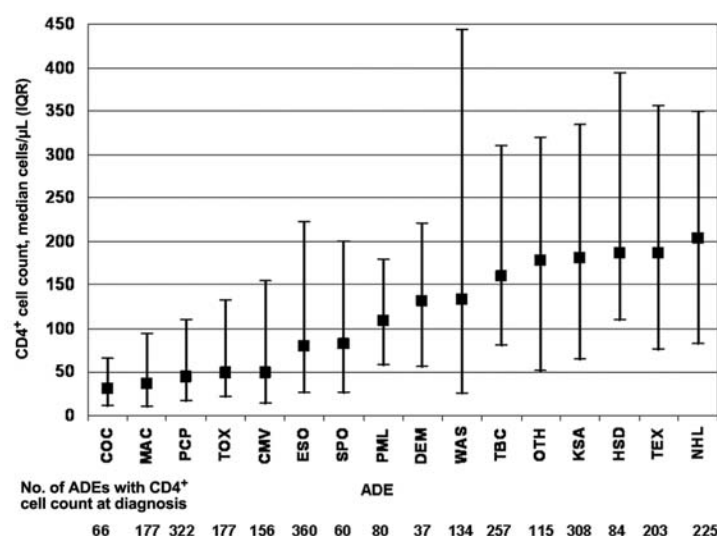
Statistical analyses were performed using SAS, version 9.1

(SAS). Bootstrapping was performed using Stata software, version 10.0 (StataCorp).

## RESULTS

The characteristics of the 31,620 patients included in analyses are shown in table 1. Over a median follow-up period of 43 months (interquartile range [IQR], 19–70 months; 117,986 person-years of follow-up), 1146 patients (3.6%) died; of these patients, 377 died after an ADE. There were 2262 patients (7.2%) who received diagnoses of 2880 distinct ADEs. A total of 1745 (77.1%) of these 2262 patients received a diagnosis of 1 ADE during follow-up, 356 (15.7%) received diagnoses of 2 ADEs, 95 (4.2%) received diagnoses of 3 ADEs, and 22 (1.0%) received diagnoses of  $\geq 4$  ADEs. The most commonly diagnosed ADEs were esophageal candidiasis (360 diagnoses), *Pneumocystis jirovecii* (carinii) pneumonia (322 diagnoses), Kaposi sarcoma (308 diagnoses), pulmonary tuberculosis (257 diagnoses) and non-Hodgkin's lymphoma (225 diagnoses).

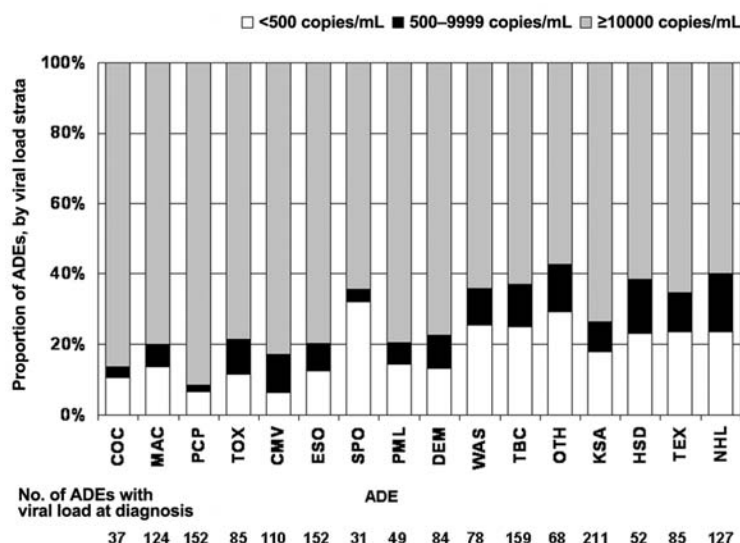
The CD4<sup>+</sup> cell count at the time of diagnosis of each ADE (available for 2635 [91.5%] of the ADEs), was measured a median of 4 days before the ADE (IQR, 0–32 days). The median CD4<sup>+</sup> cell count was 104 cells/ $\mu$ L (IQR, 32–247 cells), with 891



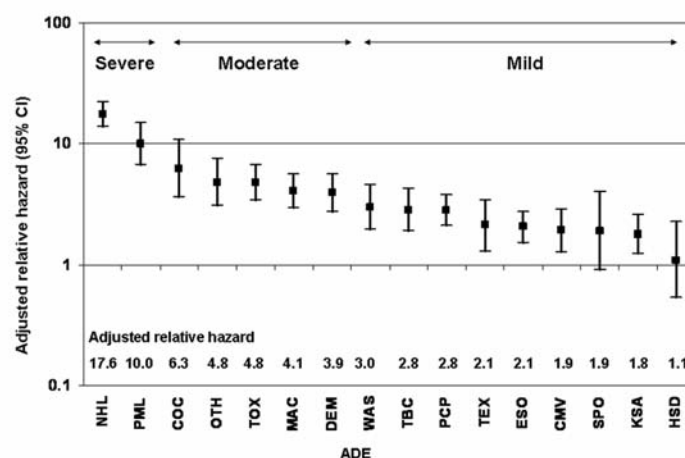
**Figure 1.** Median patient CD4<sup>+</sup> cell count at diagnosis (interquartile range [IQR]) for each type of AIDS-defining event (ADE). COC, cryptococcosis; CMV, cytomegalovirus infection; DEM, AIDS dementia complex; ESO, esophageal candidiasis; HSD, herpes simplex disease; KSA, Kaposi's sarcoma; MAC, disseminated mycobacterial disease; NHL, non-Hodgkin's lymphoma (including primary brain lymphoma); OTH, all ADEs that occurred in <50 patients; PCP, *Pneumocystis jirovecii* (carinii) pneumonia; PML, progressive multifocal leukoencephalopathy; SPO, cryptosporidiosis; TBC, pulmonary tuberculosis; TEX, extrapulmonary tuberculosis; TOX, cerebral toxoplasmosis; WAS, HIV wasting syndrome.

(33.8%) of the 2635 ADEs with available data occurring at a CD4<sup>+</sup> cell count of  $\leq 50$  cells/ $\mu$ L, 924 (35.1%) occurring at 51–200 cells/ $\mu$ L, 412 (15.6%) occurring at 201–350 cells, 189 (7.2%) occurring at 351–500 cells/ $\mu$ L, and 219 (8.3%) occurring at >500 cells/ $\mu$ L. Figure 1 illustrates the CD4<sup>+</sup> cell counts at

diagnosis, stratified by the type of ADE. Non-Hodgkin's lymphoma occurred at the highest median CD4<sup>+</sup> cell count (204 cells/ $\mu$ L), with only 34 (16.4%) of the diagnoses made in patients with CD4<sup>+</sup> cell counts  $\leq 50$  cells/ $\mu$ L. The viral load at diagnosis of each ADE (available for 1649 [57.3%] of the ADEs)



**Figure 2.** AIDS-defining events (ADEs) stratified by patient viral load at diagnosis of each type of ADE. COC, cryptococcosis; CMV, cytomegalovirus infection; DEM, AIDS dementia complex; ESO, esophageal candidiasis; HSD, herpes simplex disease; KSA, Kaposi's sarcoma; MAC, disseminated mycobacterial disease; NHL, non-Hodgkin's lymphoma (including primary brain lymphoma); OTH, all ADEs that occurred in <50 patients; PCP, *Pneumocystis jirovecii* (carinii) pneumonia; PML, progressive multifocal leukoencephalopathy; SPO, cryptosporidiosis; TBC, pulmonary tuberculosis; TEX, extrapulmonary tuberculosis; TOX, cerebral toxoplasmosis; WAS, HIV wasting syndrome.



**Figure 3.** Adjusted mortality hazard associated with each type of AIDS-defining event (ADE) after initiation of combination antiretroviral therapy (cART). The model was stratified by cohort and adjusted for age, sex, exposure group, number of drugs in the initial cART regimen, type of cART regimen, date of cART initiation, and patient CD4<sup>+</sup> cell count and viral load at cART initiation. COC, cryptococcosis; CMV, cytomegalovirus infection; DEM, AIDS dementia complex; ESO, esophageal candidiasis; HSD, herpes simplex disease; KSA, Kaposi's sarcoma; MAC, disseminated mycobacterial disease; NHL, non-Hodgkin's lymphoma (including primary brain lymphoma); OTH, all ADEs that occurred in <50 patients; PCP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; SPO, cryptosporidiosis; TBC, pulmonary tuberculosis; TEX, extrapulmonary tuberculosis; TOX, cerebral toxoplasmosis; WAS, HIV wasting syndrome.

was measured a median of 35 days before the ADE (IQR, 6–77 days). In total, 285 (17.3%) of the 1649 ADEs with available data occurred at viral loads <500 copies/mL, 154 (9.3%) occurred at 500–9999 copies/mL, and 1210 (73.4%) occurred at

≥10000 copies/mL. The distribution of the ADEs, stratified by viral load category at diagnosis, is shown in figure 2.

The median time from initiation of cART to diagnosis of ADE was 9 months (IQR, 2–30 months); 1281 (44.5%), 317

**Table 2. Ranking and classification of AIDS-defining events (ADEs) according to severity (impact on subsequent mortality) in antiretroviral-naïve patients initiating combination antiretroviral therapy.**

ADE	Median rank (2.5th and 97.5th percentiles)	ADE severity category
Non-Hodgkin's lymphoma	16 (15–16)	Severe
Progressive multifocal leukoencephalopathy	15 (13–16)	Severe
Cryptococcosis	14 (8–15)	Moderate
Cerebral toxoplasmosis	12 (6–14)	Moderate
Rare ADE <sup>a</sup>	12 (8–14)	Moderate
AIDS dementia complex	11 (6–14)	Moderate
Disseminated <i>Mycobacterium avium</i> disease	11 (6–14)	Moderate
HIV wasting syndrome	8 (2–13)	Mild
Pulmonary tuberculosis	7 (3–12)	Mild
<i>Pneumocystis jirovecii</i> (carinii) pneumonia	7 (3–11)	Mild
Extrapulmonary tuberculosis	5 (1–10)	Mild
Esophageal candidiasis	5 (2–9)	Mild
Cryptosporidiosis	4 (1–12)	Mild
Cytomegalovirus infection	4 (1–9)	Mild
Kaposi sarcoma	3 (1–8)	Mild
Herpes simplex disease	1 (1–8)	Mild

**NOTE.** Ranking is based on multivariate hazard ratios from bootstrap analyses ( $n = 1000$ ).

<sup>a</sup> Rare ADEs were defined as those that occurred in <50 patients and included coccidioidomycosis, pulmonary candidiasis, extrapulmonary pneumocystis disease, histoplasmosis, invasive cervical carcinoma, isosporiasis, salmonella septicaemia, and bacterial pneumonia.



**Table 3. Number of AIDS-defining events (ADEs) and deaths overall and within the first 6 months after initiation of combination antiretroviral therapy (cART) and adjusted mortality hazard ratios (aMHRs) associated with ADEs diagnosed after 6 months of therapy in previously antiretroviral-naïve patients.**

ADE	No. (%) of all ADEs	No. of deaths	No. (%) of ADEs diagnosed within 6 months after cART initiation	No. of deaths within 6 months after cART initiation	aMHRs associated with ADEs diagnosed after 6 months of therapy <sup>a</sup> (95% CI)
Non-Hodgkin's lymphoma	225 (7.8)	86	88 (40.4)	31	11.62 (8.69–15.54)
Progressive multifocal leukoencephalopathy	80 (2.8)	27	44 (55.0)	12	9.41 (5.90–15.02)
Cryptococcosis	66 (2.3)	14	30 (45.4)	6	4.33 (2.11–8.90)
Rare ADE <sup>b</sup>	168 (5.8)	32	76 (45.2)	11	2.94 (1.61–5.40)
Cerebral toxoplasmosis	177 (6.2)	41	69 (39.0)	12	4.11 (2.78–6.08)
Disseminated <i>Mycobacterium avium</i> disease	177 (6.2)	45	107 (61.6)	21	2.68 (1.79–4.02)
AIDS dementia complex	137 (4.8)	41	69 (50.4)	20	3.60 (2.39–5.43)
HIV wasting syndrome	134 (4.7)	29	48 (35.8)	13	2.89 (1.73–4.83)
Pulmonary tuberculosis	257 (8.9)	30	116 (45.1)	11	2.39 (1.46–3.89)
<i>Pneumocystis jirovecii</i> (carinii) pneumonia	322 (11.2)	57	127 (39.4)	15	2.36 (1.66–3.36)
Extrapulmonary tuberculosis	203 (7.1)	21	93 (45.8)	6	1.37 (0.75–2.48)
Esophageal candidiasis	360 (12.5)	69	111 (30.8)	16	1.84 (1.32–2.56)
Cytomegalovirus infection	122 (4.2)	25	66 (54.1)	8	1.60 (0.99–2.61)
Cryptosporidiosis	60 (2.1)	8	20 (33.3)	1	2.14 (0.93–4.94)
Kaposi sarcoma	308 (10.7)	33	176 (57.1)	16	1.33 (0.84–2.12)
Herpes simplex disease	84 (2.9)	9	36 (42.9)	3	0.97 (0.44–2.14)

<sup>a</sup> Comparing the hazard of death after each of the ADEs with the hazard of death among patients who have not experienced an ADE. Multivariate Cox proportional hazards models were stratified by center and adjusted for sex, exposure group, age, CD4<sup>+</sup> cell count and viral load at initiation of cART, type of regimen initiated, and date of initiation.

<sup>b</sup> Rare ADEs were defined as those that occurred in <50 patients and included coccidioidomycosis, pulmonary candidiasis, extrapulmonary pneumocystis disease, histoplasmosis, invasive cervical carcinoma, isosporiasis, salmonella septicaemia, and bacterial pneumonia.

(11.0%), 405 (14.1%), 495 (17.2%) and 382 (13.3%) of the ADEs occurred ≤6 months, 6–12 months, 12–24 months, 24–48 months, and >48 months after cART initiation, respectively. The median CD4<sup>+</sup> cell count at diagnosis for ADEs that occurred ≤6 months after cART initiation (based on data available for 1269 [48.2%] of the ADEs) was slightly lower (86 cells/μL; IQR, 30–204 cells/μL) than that for ADEs that occurred after 6 months (129 cells/μL; IQR, 35–288 cells/μL). The majority of ADEs that were diagnosed within 6 months after cART initiation occurred in patients with viral loads ≥10,000 copies/mL (1048 [83.3%] of 1258 ADEs with data), whereas almost one-half of the ADEs diagnosed after 6 months occurred in patients with viral loads of <500 copies/mL (176 [45.0%] of 391 ADEs with data).

The aMHR associated with the diagnosis of any ADE was 3.45 (95% CI, 2.75–4.32). Figure 3 illustrates the aMHR associated with each ADE, ordered from the least severe to the most severe. At one end of the spectrum, there was little evidence for an increased risk of death associated with recurrent herpes simplex disease, with an aMHR of 1.09 (95% CI, 0.53–2.25). At the other end of the spectrum, a diagnosis of non-Hodgkin's lymphoma was associated with an 18-fold increase in mortality (aMHR, 17.59; 95% CI, 13.84–22.35), whereas progressive multifocal leukoencephalopathy was associated with

a 10-fold increase in mortality (aMHR, 10.00; 95% CI, 6.70–14.92). Cryptococcosis, cerebral toxoplasmosis, the group of rare ADEs, AIDS dementia complex, and disseminated *Mycobacterium avium* complex were the next most serious events, with aMHRs of 4–7. The ranks of the aMHR for each ADE, with bootstrapped 95% CIs, are shown in table 2. As would be expected, there was considerable sampling variability in the ranks, but 3 groups of ADEs could be identified: severe (non-Hodgkin's lymphoma and progressive multifocal leukoencephalopathy), moderate (disseminated *M. avium* complex, AIDS dementia complex, rare ADEs, toxoplasmosis, and cryptococcosis), and mild (all other ADEs). The aMHR associated with any severe ADE was 7.26 (95% CI, 5.55–9.48), the aMHR associated with a moderate ADE was 2.35 (95% CI, 1.76–3.13), and the aMHR associated with a mild ADE was 1.47 (95% CI, 1.08–2.00).

There were some differences between the ADEs in terms of the proportion of diagnoses that occurred within the initial 6 months of cART (table 3), ranging from 30.8% for esophageal candidiasis to 61.6% for disseminated *M. avium* complex. Table 3 also presents the aMHR after the initial 6 months of cART, adjusted additionally for the CD4<sup>+</sup> cell count and viral load at 6 months after cART initiation and taking account of the initial response to cART. Although 95% CIs are wider because of the

reduced number of ADEs, patterns of mortality are similar to those seen in figure 3 and table 2.

## DISCUSSION

AIDS was first defined in the 1980s for surveillance purposes. However, in the era of cART, AIDS continues to be used as a composite outcome in clinical research and a prognostic marker in routine clinical care. Clinical trials that use outcome data assume that all ADEs have similar impacts on survival. The analyses presented here, which are based on >31,000 patients and almost 3000 ADEs, demonstrate substantial variation both in the median CD4<sup>+</sup> cell count at diagnosis of different ADEs and in the relative hazard of death after the diagnosis. We identified 3 groups of ADEs, based on the prognosis after diagnosis: severe ADEs, which are associated with a substantial increase in the risk of death; ADEs with a moderate impact on subsequent mortality; and mild ADEs, which have a relatively small influence on subsequent mortality.

The large size of the collaborative database, which includes patients treated in different settings in countries from Europe and North America, is a strength of this study. ADEs were ranked before the widespread introduction of cART [18, 19], but to our knowledge, this is the first study with sufficient power to enable most ADEs to be compared only among patients who have started cART. Previous studies that have considered survival after an initial ADE included only those patients who received a diagnosis of an ADE and included a significant proportion of patients who received a diagnosis of AIDS between 1990 and 1995 (when the widespread introduction of cART occurred) [20–22] or who received a diagnosis before cART became widely available [23]. This analysis thus makes an important contribution to defining the prognosis of patients who developed an ADE while receiving cART. Such information is of obvious importance to patients and their health care providers and is required to monitor and predict the progress of the epidemic, as well as to plan health services in the era of cART [24].

The initial immunologic response to cART is important for predicting prognosis after cART initiation [25]; in this study, ADEs diagnosed within 6 months after cART initiation typically occurred at slightly lower CD4<sup>+</sup> cell counts than did ADEs that were diagnosed >6 months after cART initiation, which is consistent with the recovery of immune function subsequent to starting cART. The so-called immune reconstitution inflammatory syndrome occurs when the immune system begins to respond to preexisting opportunistic disorders that were present before initiation of antiretroviral therapy [26]. We have also presented the aMHRs, both from the time of cART initiation and from after the initial 6 months of therapy. In different circumstances, it may be appropriate to use either the post-cART initiation data (which represents a combination of

immunocompromise, disease severity, and treatment effectiveness) or the pre-cART initiation data (which generally reflects untreated or poorly treated ADEs and, therefore, represents immunocompromise more specifically).

The use of composite end points, such as AIDS, in clinical trials can be advantageous: combined end points result in higher event rates, which translate into a smaller sample size, shorter trial duration, or greater precision of estimates; disease progression can then be measured either as progression to any ADE or progression to a more serious ADE. Composite end points could also be used as a predefined secondary end point or incorporated into sensitivity analyses. However, the validity of composite end points rests on the assumption that patients and clinicians attach a similar importance to the different components and that these components will be affected in similar ways by interventions [27–29]. Combining different ADEs as a single event means that important prognostic information is lost. Although the groupings proposed here were assigned post hoc, our results confirm the findings of previous smaller studies that integrated the severity of an ADE into ranking systems [30, 31], rather than treating all ADEs equally. It is also worth noting that the ranking of the diseases in the cART treatment era matches well with the ranking of diagnoses made before the widespread introduction of cART [32]. Although our classification by severity overcomes some of the drawbacks of the composite end point AIDS, what we propose are 3 composite outcomes that include a varying number of ADEs that have a similar impact on mortality. From the perspective of patients, ADEs continue to differ in important ways within the same prognostic group. For example, within the group of ADEs associated with moderately increased risk of death, AIDS dementia complex may well be judged to be more severe than the other events in this group. Similarly, it seems unlikely that the biologically diverse conditions within each group will be affected in the same way by antiretroviral drugs or other interventions.

There are some limitations to this study. Patients who died after an ADE may not have died of causes that were directly associated with the ADE that was diagnosed. The ART-CC is currently collecting information on causes of death for all patients and is using this information to categorize causes of death when possible. Preliminary data suggest that, of those patients whose cause of death could be classified, ~40% died of AIDS. The major non-AIDS causes of death among these patients were non-AIDS-defining malignancies, violent causes (including suicide and substance abuse), heart disease, and liver disease. Detailed information on the causes of death among ART-CC patients will be presented in a separate article.

The ART-CC does not collect information on coinfections, such as hepatitis, cardiovascular disease, non-AIDS-defining malignancies, or liver disease, that also contribute to mortality

[33–35]. We were not able to adjust for immunodeficiency or treatment interruptions throughout the follow-up period; however, the risk of death among HIV-infected patients increases as the CD4<sup>+</sup> cell count decreases [36, 37]. Results were similar when the initial response to cART was taken into account by adjusting for CD4<sup>+</sup> cell count and HIV RNA level at 6 months after initiation of therapy. The data were from a number of cohorts, and there is some variation in the ascertainment of ADEs. This analysis focused on the first ADE experienced after cART initiation, and the rankings could vary if recurrences were included. Finally, despite the large size of the collaborative cohort, the number of some types of ADEs was too small to allow separate analyses of these events.

In conclusion, in the cART era, mortality rates after an ADE depend on the specific ADE diagnosed, and not all ADEs are created equal. The severity of ADEs should be considered in clinical trials with clinical end points and in future prognostic models, as well as in patient management. Similar studies are required in lower-income settings, where cART is increasingly used but where outcomes differ from those observed in industrialized settings [38].

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## APPENDIX

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